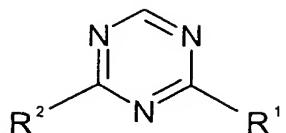


Claims

What is claimed is:

- 5 1. A compound having the formula:



wherein,

Each R¹ and R² is independently R³; R⁸; NHR³; NHR⁵; NHR⁶; NR⁵R⁵; NR⁵R⁶; SR⁵; SR⁶; SR³; OR⁵; OR⁶; OR³; C(O)R³; heterocyclyl optionally substituted with 10 1-4 independent R⁴ on each ring; or C1-C10 alkyl substituted with 1-4 independent R⁴;

Each R³ is independently aryl; phenyl optionally substituted with 1-5 independent R⁴ on each ring; or heteroaryl optionally substituted with 1-4 independent R⁴ on each ring;

Each n is independently 1 or 2;

15 Each m is independently 0, 1, 2, 3, or 4;

Each R⁴ is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; CF₃; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; NR⁵R¹⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)C(O)R⁵; NR⁵C(O)R⁵; NR⁵(COOR⁵); NR⁵C(O)R⁸; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁵; NR⁵S(O)_nR⁸; NR⁵C(O)C(O)NR⁵R⁵; NR⁵C(O)C(O)NR⁵R⁶; OC(O)NR⁵R⁵; OS(O)_nNR⁵R⁵; NR⁵S(O)_nOR⁵; P(O)(OR⁵)₂; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

25 Each R⁵ is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁹; haloalkyl; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁹ groups; C3-C10 cycloalkyl substituted

with 1-3 independent aryl, R⁷ or R⁹ groups; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁹;

Each R⁶ is independently C(O)R⁵, COOR⁵, C(O)NR⁵R⁵, C(N R⁵) NR⁵R⁵, or S(O)_n R⁵;

5 Each R⁷ is independently halo, CF₃, SR¹⁰, OR¹⁰, OC(O)R¹⁰, NR¹⁰R¹⁰, NR¹⁰R¹¹, NR¹¹R¹¹, COOR¹⁰, NO₂, CN, C(O)R¹⁰, OC(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹⁰, N(R¹⁰)C(O)R¹⁰, N(R¹⁰) (COOR¹⁰), S(O)_nNR¹⁰R¹⁰; NR¹⁰S(O)_nNR¹⁰R¹⁰; NR¹⁰S(O)_nR¹⁰; or P(O)(OR⁵)₂;

10 Each R⁸ is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2, 3 or 4 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 15 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁹; halo; sulfur; oxygen; CF₃; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; NR⁶R⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)NR⁵R⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)R⁹; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁹; C1-C10 alkyl substituted with 1-3 independent R⁷, R⁹ or aryl; or C2-C10 alkenyl substituted with 1-3 independent R⁷, R⁹ or aryl;

20 Each R⁹ is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent independently 25 selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; halo; sulfur; oxygen; CF₃; haloalkyl; SR¹⁰; OR¹⁰; NR¹⁰R¹⁰; NR¹⁰R¹¹; NR¹¹R¹¹; COOR¹⁰; NO₂; CN; C(O)R¹⁰; S(O)_nR¹⁰; S(O)_nNR¹⁰R¹⁰; or C(O)NR¹⁰R¹⁰;

30 Each R¹⁰ is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; haloalkyl; C1-C10 alkyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-

C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹², SR¹², NR¹²R¹², COOR¹², NO₂, CN, C(O)R¹², C(O)NR¹²R¹², NR¹²C(O)R¹², N(R¹²)(COOR¹²), S(O)_nNR¹²R¹², or OC(O)R¹²; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹², SR¹², NR¹²R¹², COOR¹², NO₂, CN, C(O)R¹², C(O)NR¹²R¹², NR¹²C(O)R¹², N(R¹²)(COOR¹²), S(O)_nNR¹²R¹², or OC(O)R¹²;

Each R¹¹ is independently C(O)R¹⁰, COOR¹⁰, C(O)NR¹⁰R¹⁰ or S(O)_nR¹⁰;

Each R¹² is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl substituted with 1-3 independent C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹³, SR¹³, NR¹³R¹³, COOR¹³, NO₂, CN, C(O)R¹³, C(O)NR¹³R¹³, NR¹³C(O)R¹³, or OC(O)R¹³; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹³, SR¹³, NR¹³R¹³, COOR¹³, NO₂, CN, C(O)R¹³, C(O)NR¹³R¹³, NR¹³C(O)R¹³, or OC(O)R¹³;

Each R¹³ is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl optionally substituted with halo, CF₃, OR¹⁴, SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN; or phenyl optionally substituted with halo, CF₃, OR¹⁴, SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN;

Each R¹⁴ is independently H; C1-C10 alkyl; C3-C10 cycloalkyl or phenyl;

Each R¹⁵ is independently H; CF₃; CN; COOR⁵; or C1-C10 alkyl substituted with 1-3 independent OR⁵, SR⁵, or NR⁵R⁵;

Each R¹⁶ is independently H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; CF₃; COOR⁵; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷, R⁸, or phenyl optionally substituted with substituted with 1-4 independent R²³; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

Each R¹⁷ is independently NR⁵R¹⁶; OR⁵; SR⁵; or halo;

Each R¹⁸ is independently C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; CF₃; COOR⁵; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

5 Each R¹⁹ is independently H or C1-C6 alkyl;

 Each R²⁰ is independently NR⁵R¹⁸; OR⁵; SR⁵; or halo;

 Each R²¹ is independently t-butyl, 4-carboxyphenyl, 4-carbomethoxyphenyl, or furyl substituted with 1-4 independent R⁴;

10 Each R²² is independently C2-C9 alkyl substituted with 1-2 independent aryl, R⁷, or R⁸;

 Each R²³ is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; CF₃; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)C(O)R⁵; NR⁵C(O)R⁵; NR⁵(COOR⁵); NR⁵C(O)R⁸; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁵; NR⁵S(O)_nR⁸; NR⁵C(O)C(O)NR⁵R⁵; NR⁵C(O)C(O)NR⁵R⁶; OC(O)NR⁵R⁵; OS(O)_nNR⁵R⁵; NR⁵S(O)_nOR⁵; P(O)(OR⁵)₂; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

15 Each R²⁴ is independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁹; halo; sulfur; oxygen; CF₃; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; NR⁶R⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)NR⁵R⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)R⁹; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁹; C1-C10 alkyl substituted with 1-3 independent R⁷, R⁹ or aryl; or C2-C10 alkenyl substituted with 1-3 independent R⁷, R⁹ or aryl;

20 Each X is independently O or S;

 Each V, W, Y, and Z is independently N or CR⁴;

Each haloalkyl is independently a C1-C10 alkyl substituted with one or more halogen atoms, selected from F, Cl, Br, or I, wherein the number of halogen atoms may not exceed that number that results in a perhaloalkyl group;

Each aryl is independently a 6-carbon monocyclic, 10-carbon bicyclic or 5 14-carbon tricyclic aromatic ring system optionally substituted with 1-3 independent C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; R⁹; halo; haloalkyl; CF₃; OR¹⁰; SR¹⁰; NR¹⁰R¹⁰; NR¹⁰R¹¹; COOR¹⁰; NO₂; CN; C(O)R¹⁰; C(O)C(O)R¹⁰; C(O)NR¹⁰R¹⁰; N(R¹⁰)C(O)NR¹⁰R¹⁰; N(R¹⁰)C(O)R¹⁰; N(R¹⁰)S(O)_nR¹⁰; N(R¹⁰)(COOR¹⁰); NR¹⁰C(O)C(O)R¹⁰; NR¹⁰C(O)R⁹; NR¹⁰S(O)_nNR¹⁰R¹⁰; NR¹⁰S(O)_nR⁹; 10 NR¹²C(O)C(O)NR¹²R¹²; S(O)_nR¹⁰; S(O)_nNR¹⁰R¹⁰; OC(O)R¹⁰; C1-C10 alkyl substituted with 1-3 independent R⁹, halo, CF₃, OR¹⁰, SR¹⁰, OC(O)R¹⁰, NR¹¹R¹¹, NR¹⁰R¹⁰, NR¹⁰R¹¹, COOR¹⁰, NO₂, CN, C(O)R¹⁰, OC(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹⁰, N(R¹⁰)C(O)R¹⁰, N(R¹⁰)(COOR¹⁰), S(O)_nNR¹⁰R¹⁰; R¹⁰; or C2-C10 alkenyl substituted with 1-3 independent R⁹, halo, CF₃, OR¹⁰, SR¹⁰, OC(O)R¹⁰, NR¹¹R¹¹, NR¹⁰R¹⁰, NR¹⁰R¹¹, COOR¹⁰, NO₂, CN, 15 C(O)R¹⁰, OC(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹⁰, N(R¹⁰)C(O)R¹⁰, N(R¹⁰)(COOR¹⁰), S(O)_nNR¹⁰R¹⁰;

Each heterocyclyl is independently a 3-8 membered nonaromatic monocyclic, 8-12 membered nonaromatic bicyclic, or 11-14 membered nonaromatic tricyclic, ring system comprising 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if 20 bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S; and

Each heteroaryl is independently a 5-8 membered aromatic monocyclic, 8-25 12 membered aromatic bicyclic, or 11-14 membered aromatic tricyclic ring system comprising 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S.

2. The compound of claim 1 wherein,

R¹ is independently R³; and

30 R² is independently NHR³.

3. The compound of claim 1 wherein,

R^1 is independently heteroaryl optionally substituted with 1-4 independent R^4 on each ring; and

R^2 is independently NHR^3 .

5

4. The compound of claim 1 wherein,

R^1 is independently phenyl optionally substituted with 1-5 independent R^4 ;

and

R^2 is independently NHR^3 .

10

5. The compound of claim 1 wherein,

Each R^1 and R^2 is independently NHR^3 .

15

6. The compound of claim 1 wherein,

R^1 is independently NHR^5 ; and

R^2 is independently NHR^3 .

20

7. The compound of claim 1 wherein,

R^1 is independently NHR^6 ; and

R^2 is independently NHR^3 .

25

8. The compound of claim 1 wherein,

R^1 is independently OR^5 ; and

R^2 is independently NHR^3 .

30

9. The compound of claim 1 wherein,

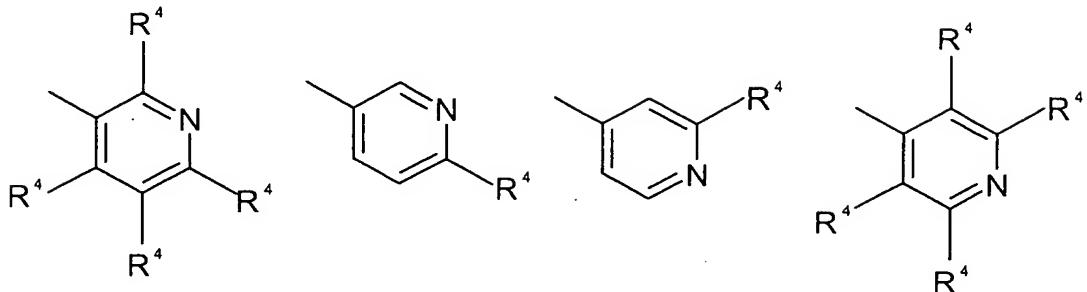
R^1 is independently SR^5 ; and

R^2 is independently NHR^3 .

10. The compound of claim 1 wherein:

R^2 is independently NHR^3 ; and

R^1 is one of the following groups:



5

10 11. The compound of claim 1 wherein,

R^1 is independently heterocyclyl optionally substituted with 1-4 independent R^4 on each ring, wherein said heterocyclyl is not unsubstituted piperidine; and

R^2 is independently NHR^3 .

15

12. The compound of claim 1 wherein,

Each R^1 is independently heteroaryl substituted with 1-4 independent R^4 on each ring, wherein said heteroaryl comprises at least one nitrogen heteroatom and said 20 heteroaryl is attached at said nitrogen heteroatom; and

Each R^2 is independently NHR^3 .

25

13. The compound of claim 1 wherein,

Each R^1 is independently heterocyclyl substituted with 1-4 independent R^4 on each ring, wherein said heterocyclyl is not unsubstituted piperidine, and said

heterocyclyl comprises at least one nitrogen heteroatom and said heterocyclyl is attached at said nitrogen heteroatom; and

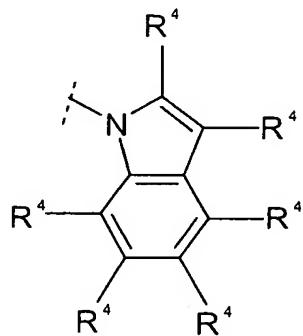
Each R² is independently NHR³.

5

14. The compound of claim 1 wherein,

Each R² is independently NHR³; and

Each R¹ is independently of the formula:



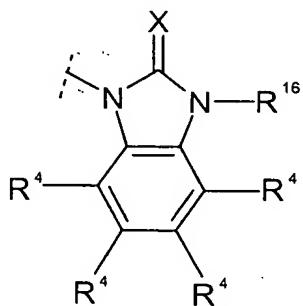
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15. The compound of claim 1 wherein,

Each R² is independently NHR³; and

Each R¹ is independently of the formula:

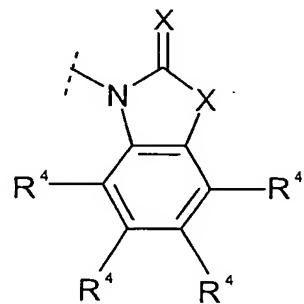
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16. The compound of claim 1 wherein,

Each R² is independently NHR³; and

Each R¹ is independently of the formula:

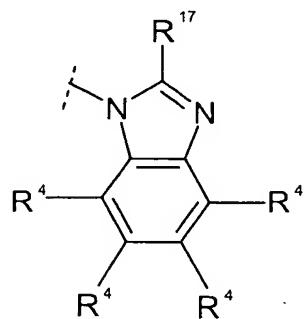


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17. The compound of claim 1 wherein,

Each R² is independently NHR³; and

Each R¹ is independently of the formula:

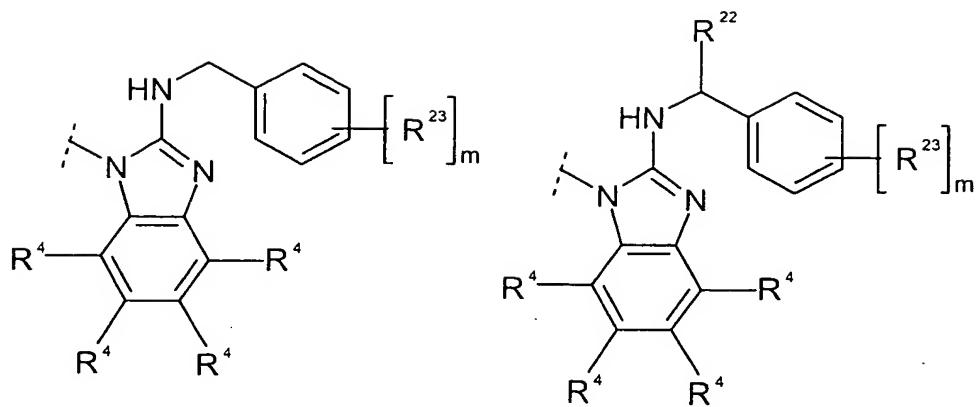


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18. The compound of claim 1 wherein,

Each R¹ is independently one of the following groups:

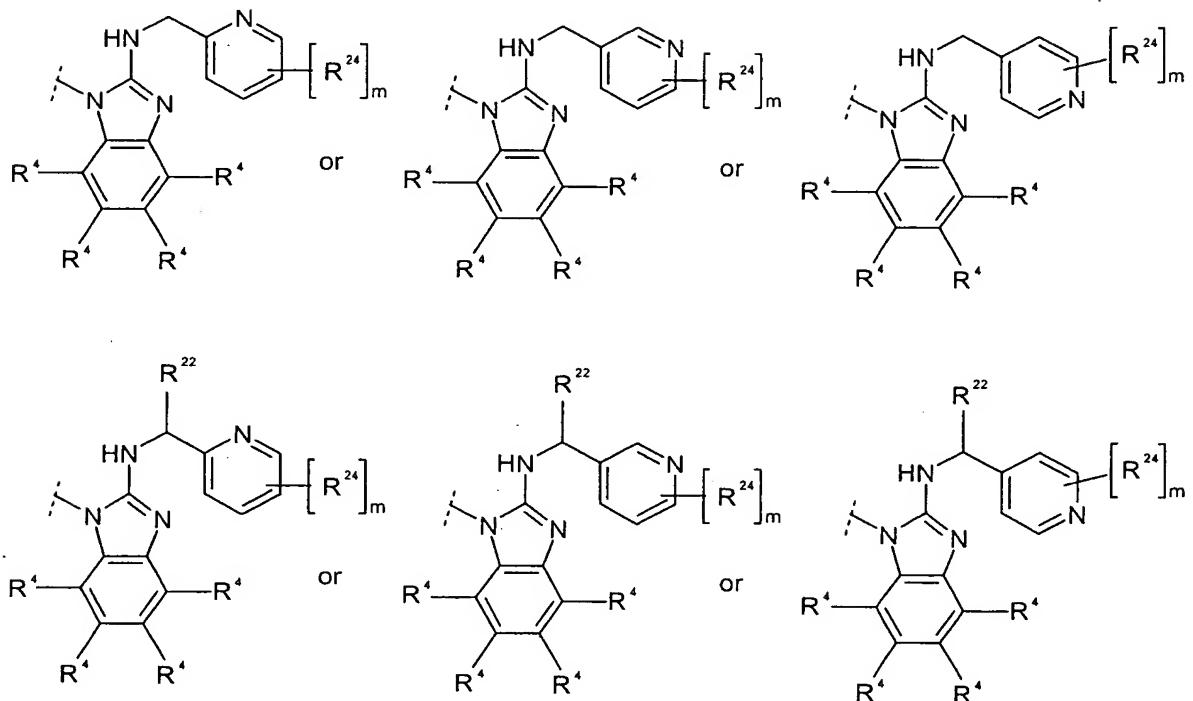
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wherein m is 0, 1, 2, 3 or 4.

5 19. The compound of claim 1 wherein,

Each R¹ is independently

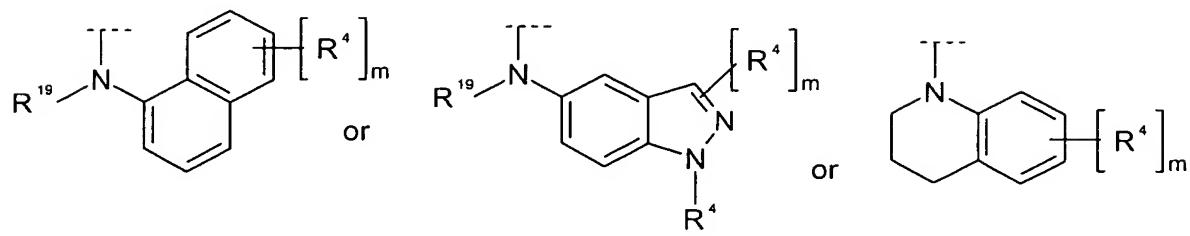
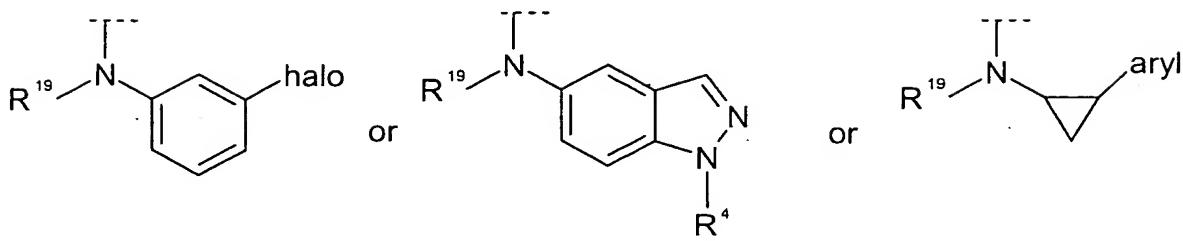


wherein m is 0, 1, 2, 3 or 4.

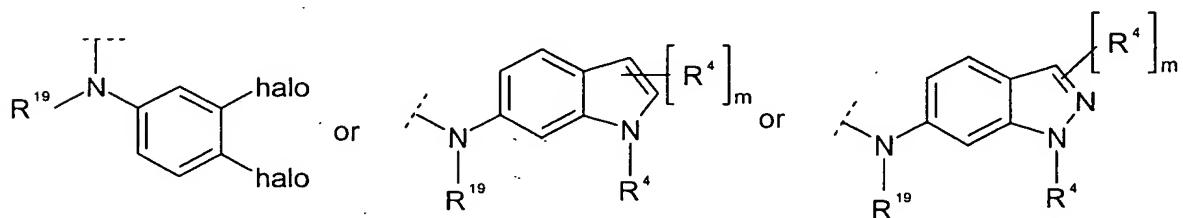
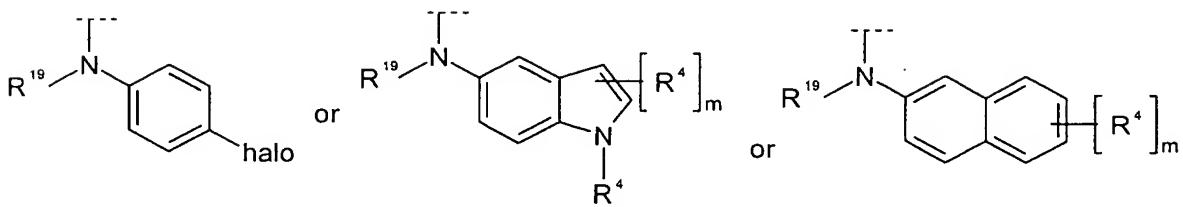
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20. The compound of claim 1 wherein,

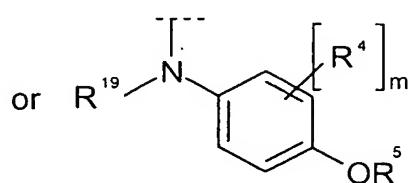
Each R¹ is independently one of the following:



5



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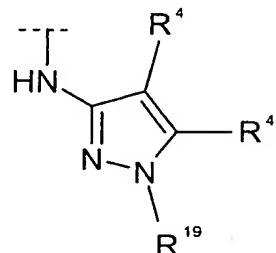


wherein the groups are as defined in claim 1.

21. The compound of claim 1 wherein,

5

Each R¹ is independently



wherein R¹⁹ is independently H or C1-C6 alkyl.

22. A composition comprising a compound of any of claims 1-21 and a
10 pharmaceutically acceptable carrier.

23. The composition of claim 22, further comprising at least one additional
therapeutic agent.

15

24. A method of treating kinase-mediated disease or disease symptoms in a
mammal comprising administration of a composition comprising a compound of any of
claims 1-21.

20

25. A method of inhibiting kinase activity in a mammal comprising administration
of a composition comprising a compound of any of claims 1-21.

25

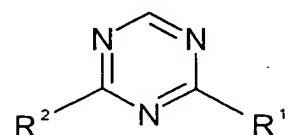
26. A method of treating disease or disease symptoms in a mammal comprising
administration of a composition comprising a compound of any of claims 1-21.

27. A method of inhibiting angiogenesis or vasculogenesis activity in a mammal comprising administration of a composition comprising a compound of any of claims 1-21.

5 28. A method of making a pharmaceutically useful composition comprising combining a compound of any of claims 1-21 with one or more pharmaceutically acceptable carriers.

10 29. The method of claim 28, further comprising combining an additional therapeutic agent.

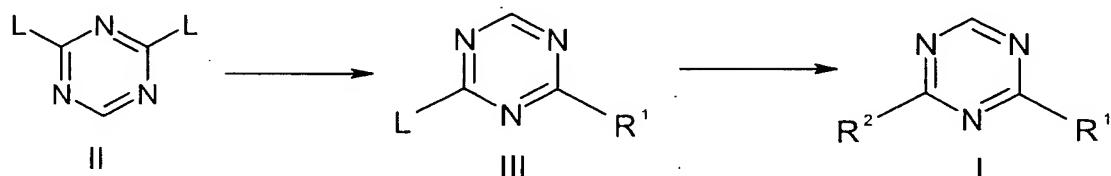
30. A method of making a compound of claim 1 of the formula



wherein

15 Each R¹ and R² is independently R³; R⁸; NHR³; NHR⁵; NHR⁶; NR⁵R⁵; NR⁵R⁶; SR⁵; SR⁶; SR³; OR⁵; OR⁶; OR³; C(O)R³; heterocyclyl optionally substituted with 1-4 independent R⁴ on each ring; or C1-C10 alkyl substituted with 1-4 independent R⁴;

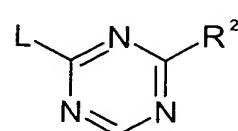
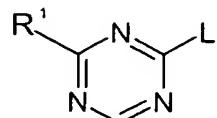
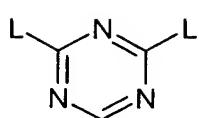
20 Each R³ is independently aryl; phenyl optionally substituted with 1-5 independent R⁴ on each ring; or heteroaryl optionally substituted with 1-4 independent R⁴ on each ring; comprising the steps of:



- a) reacting a compound of formula (II) wherein each L is independently a leaving group as defined herein, with a nucleophile of formula H-R¹ (or salt thereof) to give a compound of formula (III); and

b) reacting the compound of formula (III) with a nucleophile of formula H-R² (or salt thereof) to give a compound of formula (I).

5 31. A method of making a compound of claim 1 comprising reacting a triazine of one or more of the formulae:



10 with an appropriate nucleophilic agent or agents, wherein L is a leaving group and the other groups in said formulae are as defined in claim 1.